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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,105	10/04/2001	Ann Burchell	350013-76	4877

7590 01/02/2003

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	11

DATE MAILED: 01/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,105	BURCHELL ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1,8 and 17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/392,055* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 & 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I (claims 2-7 and 9-16) in Paper #10 filed 8/27/02 is acknowledged. Applicant does not traverse the Restriction Requirement on the grounds of lack of patentable distinctness. The traversal on the ground(s) "that a sufficient burden to require restriction does not exist and that the inventions are sufficiently related to preclude restriction notwithstanding the existence of patentable distinctness", is not found convincing. (Page 6, last paragraph-Paper #6).

This is not found persuasive because MPEP § 808.02 recites:

> Where related inventions as claimed are shown to be distinct under the criteria of MPEP § 806.05(c)- § 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof, (B) A separate status in the art when they are classified together, or (C) A different field of search.

In the instant case, (A) -The Restriction Requirement under 35 U.S.C. § 121 in Paper #9 established distinctness of the inventions and separate classification thereof:

(B) The inventions of Groups I, II, III, and IV would require a separate status in the art when they are classified together; the invention as a whole is drawn to genetic material analysis thereby identifying and isolating fetal red blood cells as an indicator of fetal abnormality. Such inventions are classified in 435, subclass 91.2 for example.

(C) With respect to a different field of search – Because these inventions are distinct and have acquired separate status in the art as shown by their different classification, recognized divergent subject matter and because the search required for each invention is not substantially coextensive with the search required for the remaining invention, restriction for examination purposes as indicated is proper. Please note that the classifications in the restriction are illustrative only and do **not** represent all the classes and subclasses which must be searched for each invention; nor is the search limited to issued US patents, but rather includes published foreign patents and applications as well as literature search.

2. Further, the combination of Groups I, II, and III (claims 1-21) for examination on the merits is deemed incorrect. The merging of these groups would combine three patentably distinct inventions: Group I - Claim 1 is directed to a method of simply identifying an embryonic or fetal red blood cell from maternal cells via the expression of an adult liver component; Group II - Claim 2 is directed to the isolation of an embryonic or fetal red blood cell – which encompasses more complex procedures beyond mere identification; such as isolation, purification, product integrity, and stability; and Group III - Claim 17 is directed to method of determining a fetal abnormality wherein correlated assessment of the liver component to normal/abnormal levels. For these reasons the inventions of Groups I, II, and III were not joined.

The Restriction Requirement is still deemed proper and is therefore made **FINAL.**

3. Currently, claims 1-23 are subject to Restriction and Election Requirement. Claims 1, and 17-23 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as claims drawn to a non-elected invention. Claims 2-7 and 9-16 are under examination.

Priority

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). This application does not contain the required first sentence of the specification referencing provisional document 60/067,520 filed 12/4/97 and foreign application No. 9704876.3 filed 3/8/97. Please add to the specification.

5. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 3/8/1997. It is noted, however, that applicant has not filed a certified copy of the (9704876.3) application as required by 35 U.S.C. 119(b).

Drawings

6. The drawings in this application are objected to by the Draftsperson as informal. Any drawing corrections requested, but not made in the prior application should be repeated in this application if such changes are still desired.

If the drawings were changed and approved during the prosecution of the prior application, a petition may be filed under 37 CFR 1.182 requesting the transfer of such drawings provided the parent application has been abandoned. However, a copy of the drawings as originally filed must be included in the 37 CFR 1.60 application papers to indicate the original content.

Information Disclosure Statement

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form PTO-1449 have cited the references they have not been considered.

8. The information disclosure statement filed 2/14/02 - Paper#5, fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each document listed that is not in the English language. The reference – Hepato-Nephromegalia Glykogenica, E.Von Gierke, p.498-513 was not considered because it did not include a certified English translation of the full document or a concise explanation of relevance. It has been placed in the application file, but the information referred to therein has not been considered.

9. The information disclosure statement filed 6/12/02 in paper #8 has been considered as to the merits prior to first action.

Specification

10. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

11. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The instant abstract includes the claim language "said". It should be eliminated in order to obviate this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 2, 6, and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 2 the use of "cell surface exposed component" is indefinite. The claim does not define the intended meaning, therein the metes and bounds of the claims can not be determined. The specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

B. Claims 6 and 7 are vague and indefinite in reciting "component" because it is not clear if applicant intends to mean the adult liver component of claim 2 or some other component. It is suggested that the claims consistently employ "adult liver component" for clarity. Appropriate correction required.

C. Claim 7 is vague and indefinite in the use of "at less than 1percent on a per cell basis". If applicant intends to claim a unit of measurement, it should be recited as such. Please define.

Double Patenting

13. Double patenting obviousness-type rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 2, 6, 9, 10, and 12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 of U.S. Patent No. 6,331,395.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to methods of isolating embryonic or fetal red blood cells via antibodies to GLUT2 (glucose transporter 2). Specifically the instant claims (2, 6, 9, 10, and 12) are drawn to a broad method of isolating embryonic or fetal red blood cells that encompasses the particular GLUT2 (glucose transporter 2) of claim 1 in patent #6,331,395. Accordingly the instant invention is encompassed in US Patent #6,331,395. It would have been obvious to the skilled practitioner in the art to employ various known adult liver components in the method of isolating embryonic or fetal red cells as an obvious modification of the known method in patent 6,331,395 because it has been held that the provision of adjustability, where needed, involves only routine skill in the art. *In re Stevens*, 101 USPQ 284 (CCPA 1954) .

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 2-4 and 6 are rejected under #5 U.S.C. 102(b) as being anticipated by Bianchi et al. (WO 91/07660).

Bianchi et al. teach a method of isolating fetal nucleated cells from maternal blood. An antigen present on the cell surface of the fetal erythrocyte is detected and related to a gene or gene portion associated with a disease or condition, a chromosomal abnormality or sex-specific DNA, in the maternal blood sample.

The method is taught to be useful in prenatal or postnatal sampling, but is particularly useful as a noninvasive method that can be employed early in pregnancy. Bianchi et al. disclose that fetal nucleated cells can be isolated or separated from maternal blood and that DNA present in the isolated fetal cells can be used to assess fetal characteristics. (Page 7, lines 19-29). Monoclonal antibodies which recognize maternal leukocytes and monoclonal antibodies which recognize fetal cell surface antigens were applied to separate maternal and fetal cells. Any monoclonal antibody (not just transferrin receptor – example 1) that distinguishes between fetal and maternal cells on the basis of surface antigenic differences can be used in this invention. (See page 9, lines 14-31 and page 12, lines 7-12).

Specifically the method involves: (pages 13 and 14)

- Obtaining a maternal blood sample, separating the sample on the basis of size and the mononuclear cell layer to produce a maternal sample enriched in nucleated cells.
- Contacting the enriched sample with at least one monoclonal antibody to result in a fetal nucleated cell/antibody complex that is separated using known methods.
- Amplifying and identifying the DNA.

II. Claims 2-4 and 6 are rejected under #5 U.S.C. 102(b) as being anticipated by Spector et al. (Am J Hum Genet. 32:79-87, 1980).

Spector et al. show the identification and isolation of a specific adult liver component (Arginase). Fetal and adult red blood cell Arginase is linked to the detection of prenatal Arginase deficiency.

Prenatal detection of Arginase deficiency has only recently been possible by obtaining fetal red blood cells largely free of maternal cells via amnioscopy and amniocentesis. Red blood cells from young children and adults have a high arginase content and the immunologic properties of human red blood cell arginase are identical with those of liver arginase. Investigators studied the biochemical and immunologic properties of arginase in the red cell from 13 to 20 week fetuses and found fetal red blood cells to be suitable for the prenatal diagnosis of Arginase deficiency. Specifically, the method involved obtaining the fetal/embryonic red blood cells, conducting an enzyme assay. The fetal red blood cell arginase differed from the adult arginase only in its total activity. The fetal red blood cells showed decreased activity when compared to the adult arginase.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 5, 7, 9-12, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bianchi et al. (WO 91/07660) or Spector et al. (Am J Hum Genet. 32;79-87,1980) in view of Hume et al. (Early Human Development, Vol.42, No.2, 1995, pp. 85-95) and Hume et al. (Blood, Vol.87, No.2, 1996, pp.762-770).

Please see previous discussions of Bianchi et al. and Spector et al.

Bianchi et al. and Spector et al. differ from the instant invention in failing to teach a method of identifying and isolating embryonic or fetal red blood cells via an adult liver protein such as the specific proteins listed in claim 9. It is noted that the specification teaches adult liver protein to be any one of a microsomal glucose-6-phosphates enzyme. (Page 8 section 0047).

However, Hume et al. (Early Human Development, Vol.42, No.2, 1995, pp. 85-95) and Hume et al. (Blood, Vol.87, No.2, 1996, pp.762-770) both teach the utility of such proteins in red blood cell detection systems/methods.

Hume et al. (Early Human Development, Vol.42, No.2, 1995, pp. 85-95) show that the microsomal glucose-6-phosphatase enzyme protein is expressed in human embryonic and fetal red blood cells. Glucose-6-phosphatase was found to be immunopositive for circulating red cells in the primitive megaloblastic series.

Hume et al. (Blood, Vol.87, No.2, 1996, pp.762-770) et al. teach that microsomal glucose-6-phosphatase catalyzes the terminal step of glycogenolysis and gluconeogenesis and is expressed predominantly in the liver. The study of the endoplasmic reticulum system involving glucose-6-phosphatase, lead investigators to study other endoplasmic reticulum proteins. These proteins included uridine diphosphate-glucuronosyltransferase, cytochrome P450 isozymes, nicotinamide adenine dinucleotide phosphatecytochrome P450 oxidoreductase, and prostaglandin H synthase.

Bianchi et al., Spector et al., Hume et al., and Hume et al., are all analogous art because they are from the same field of endeavor, all three inventions teach immunoassay techniques involving fetal red blood cells and prenatal diagnosis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the specific proteins as taught by Hume et al., and Hume et al. in the methods of Bianchi et al. or Spector et al. to perform fetal red blood cell identification and isolation assay techniques, because such proteins as taught by Hume et al., and Hume et al. are well known in the art.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such proteins, because Hume et al. (Early Human Development, Vol.42, No.2, 1995, pp. 85-95) taught that the predominantly hepatic protein (glucose-6-phosphatse) in adults is present in nucleated embryonic and fetal red blood cells and is useful in diagnosis of disorders associated with liver protein expression in the first trimester maternal circulation.

One having ordinary skill in the art would have been motivated to do this because the early detection of such disorders is both beneficial in possible treatment and early preparation/education of the fetal family for the birth of an abnormal baby.

With respect to claim 7 wherein the concentration of the detectable adult liver component is at less than 1 percent per cell basis in maternal cells. Such detection limits are viewed as mere assay optimization. Absent results to the contrary or unexpected results the modification is viewed as an obvious modification that does not render the claims patentably distinct from the prior art assay methods.

II. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bianchi et al. (WO 91/07660) or Spector et al. (Am J Hum Genet. 32;79-87,1980) in view of Hume et al. (Early Human Development, Vol.42, No.2, 1995, pp. 85-95) and Hume et al. (Blood, Vol.87, No.2, 1996, pp.762-770) as applied to claims 5, 7, 9-12, and 14-16 above, and further in view of in view of Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187).

Please see Bianchi et al. and Spector et al. in view of Hume et al. and Hume et al. as set forth above.

Bianchi et al. and Spector et al. in view of Hume et al. and Hume et al. differ from the instant invention in not specifically teaching reagent immobilization to a solid support such as micro titer plates.

However, Maggio disclose enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase. The solid phase can be particles, cellulose, polyacrylamide, agarose, discs, tubes, beads, or micro plates (micro titer plates). See page 186.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the reagents on a solid support/micro titer plates as taught by Maggio in the assay method to isolate red blood cells of Bianchi et al. and Spector et al. in view of Hume et al. and Hume et al. because Maggio taught that micro plates or micro titer plates "are very convenient for reagent immobilization and eliminate washing thereby reducing labor in assay procedures". Page 186, last line.

17. For reasons aforementioned, no claims are allowed.

Remarks

18. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Ahlert et al. (WO 93/23754-Abstract Only) teach a process for prenatal diagnosis of genetic abnormalities.

B. Chou et al. (U.S.Patent#5,460,942) disclose the catalytic moiety of the glucose-6-phosphatase system: The gene and protein and related mutations.

C. Bianchi (U.S.Patent#5,714,325) teach a method for detecting a nucleic acid of interest in a fetal nucleic acid derived from a pregnant woman.

D. Bianchi (U.S.Patent#5,641,628) teach a non-invasive method fro isolating and detecting fetal DNA.

E. Golbus (U.S.Patent#5,731,156) teach anti-embryonic hemoglobin antibodies to identify fetal nucleated erythrocytes or erythroblasts.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook

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12/23/02

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